

Acute Myocardial Infarction

Low Molecular Weight Heparin (Dalteparin) as Adjuvant Treatment to Thrombolysis in Acute Myocardial Infarction—A Pilot Study: Biochemical Markers in Acute Coronary Syndromes (BIOMACS II)

Gunnar Frostfeldt, MD, Greger Ahlberg, MD,* Gunnar Gustafsson, MD,† Gunnar Helmius, MD, PhD,‡ Bertil Lindahl, MD, PhD, Anders Nygren, MD, PhD,§ Agneta Siegbahn, MD, PhD,§ Eva Swahn, MD, PhD,|| Per Venge, MD, PhD,§ Lars Wallentin, MD, PhD

Uppsala, Falun, Gävle and Linköping, Sweden

-
- | | |
|--------------------|---|
| OBJECTIVES | This randomized, double blind, placebo-controlled pilot trial evaluated the effect of dalteparin as an adjuvant to thrombolysis in patients with acute myocardial infarction regarding early reperfusion, recurrent ischemia and patency at 24 h. |
| BACKGROUND | Low-molecular-weight heparin, given subcutaneously twice daily without monitoring, might be an attractive alternative to conventional intravenous heparin in the treatment of acute myocardial infarction. |
| METHODS | In 101 patients dalteparin/placebo 100 IU/kg was given just before streptokinase and a second injection 120 IU/kg after 12 h. Monitoring with continuous vector-ECG was done to obtain signs of early reperfusion and later ischemic episodes. Blood samples for myoglobin were obtained at start and after 90 min to evaluate signs of reperfusion. Coronary angiography was performed after 20–28 h to evaluate TIMI-flow in the infarct-related artery. |
| RESULTS | Dalteparin added to streptokinase tended to provide a higher rate of TIMI grade 3 flow in infarct-related artery compared to placebo, 68% versus 51% ($p = 0.10$). Dalteparin had no effects on noninvasive signs of early reperfusion. In patients with signs of early reperfusion, there seemed to be a higher rate of TIMI grade 3 flow, 74% versus 46% (myoglobin) ($p = 0.04$) and 73% versus 52% (vector-ECG) ($p = 0.11$). Ischemic episodes 6–24 h. after start of treatment were fewer in the dalteparin group, 16% versus 38% ($p = 0.04$). |
| CONCLUSIONS | When dalteparin was added as an adjuvant to streptokinase and aspirin, there were tendencies for less ECG monitoring evidence of recurrent ischemia and better patency at 24 h, warranting further study. (J Am Coll Cardiol 1999;33:627–33) © 1999 by the American College of Cardiology |
-

Since 1988 intravenous thrombolysis is routinely used in the treatment of acute myocardial infarction. Early successful reperfusion and maintained patency of the infarct-related artery reduces the size of the myocardial infarction, risk of cardiac insufficiency and mortality (1,2). The best results are obtained in patients treated within the first hours after onset of symptoms and with early complete restoration of flow

(TIMI3) in the infarct-related artery (3,4). Only patients without reocclusion and maintained Thrombolysis in Myocardial Infarction Trial (TIMI) grade 3 flow in the infarct-related artery have a long-term favorable effect of thrombolysis (5–7).

The additional effect of aspirin as treatment of acute myocardial infarction is today a well-established standard therapy (8,9). Heparin infusion after treatment with thrombolytic agents improves early patency in the infarct-related artery (10). However, the influences of heparin on long-term mortality is less clear (11–13). In clinical practice, heparin infusions monitored by activated partial thromboplastin time (aptt) are cumbersome and the value of appt is reduced (14). Low-molecular-weight (lmw) heparin as an adjuvant to thrombolytic treatment might be an alternative to standard intravenous heparin as it is simpler to administer and it can be given as a subcutaneous weight adjusted

From the Department of Cardiology, Cardiothoracic Centre, University Hospital, Uppsala; *Department of Medicine, Falu County Hospital, Falun; †Department of Medicine, Gävle County Hospital, Gävle; ‡Department of Diagnostic Radiology, University Hospital, Uppsala; §Department of Clinical Chemistry, University Hospital, Uppsala; ||Department of Cardiology, University Hospital, Linköping, Sweden. This study was supported by grants from the Swedish Heart-Lung Foundation and Pharmacia-Upjohn, Sweden.

Manuscript received July 6, 1998; revised manuscript received October 9, 1998, accepted November 6, 1998.

Abbreviations and Acronyms

CABG	= coronary artery bypass grafting
GUSTO	= Global Utilization of Streptokinase and t-PA for Occluded Arteries
Lmw-heparin	= low-molecular-weight heparin
PTCA	= percutaneous coronary angioplasty
STVM	= ST vector magnitude
TIMI	= Thrombolysis In Myocardial Infarction Trial

twice daily standard dose without monitoring (15,16). Therefore this treatment might be used for a longer period of time until passivation of the infarct-related coronary lesions.

In a pilot study we have investigated whether subcutaneous lmw-heparin added to streptokinase and aspirin is safe and if it improves patency and maintains TIMI grade 3 flow in infarct-related coronary arteries. We also investigated whether lmw-heparin influences postthrombolytic ischemic episodes.

PATIENTS AND METHODS

Design. This study was a prospective, multicenter, double blind, randomized and parallel-group trial. The primary aim was to investigate if dalteparin (Fragmin, Pharmacia & Upjohn, Stockholm, Sweden) has additional effects to conventional thrombolytic therapy with streptokinase on blood flow in infarct-related coronary arteries 20–28 h after start of thrombolytic treatment. Secondary aims were safety and the effects of dalteparin regarding occurrence of signs of early reperfusion and postreperfusion ischemic episodes as indicated with biochemical markers (myoglobin) and continuous vector-ECG. Other secondary aims were to evaluate the effects of dalteparin in patients with noninvasive signs of early reperfusion regarding the rate of TIMI grade 3 flow in the infarct-related arteries and postreperfusion ischemic episodes.

Patients. The patients were recruited at three Swedish hospitals between May 1993 and May 1995. Patients admitted to the Coronary Care Units with chest pain during the last 12 hours suggesting acute myocardial infarction with ST-elevation or new or previously unknown left bundle branch block were eligible for inclusion in this study.

Exclusion criteria were conditions with an increased risk of bleeding; contraindication to streptokinase; ongoing treatment with heparin or lmw-heparin; any condition that made early coronary angiography or early revascularization unsuitable or contraindicated; previous coronary artery bypass surgery; aortic stenosis with hemodynamic importance; increased risk for embolization; known renal (creatinine >200 $\mu\text{mol/L}$) or liver insufficiency (prothrombin time <50% of normal); age over 80; previous inclusion in this study or participation in another study.

Written and oral information was given, and witnessed

consent was obtained before inclusion. The study was approved by the ethics committees of both participating university hospitals and by the Swedish Medical Products Agency. All procedures followed the Declaration of Helsinki.

Randomization and the study drug. The randomization was done in blocks within each center. The first injection of the study drug dalteparin/placebo was given just before the start of thrombolysis, 100 U/kg subcutaneously. A second subcutaneous injection of 120 U/kg was given 12 h later. No further dose of dalteparin was given after evaluation of primary endpoint by coronary angiography. Maximum dose at each occasion was 10000 U.

Additional drugs. Patients previously on aspirin continued on 75 mg orally daily. Patients not previously on aspirin were given 300 mg as an oral bolus and thereafter 75 mg orally daily. Immediately after the injection of dalteparin/placebo, streptokinase was given intravenously as 1.5 million Units infusion during 60 min. Nitroglycerin infusion was started during or early after streptokinase infusion unless contraindicated and continued for at least 24 h, until and during the coronary angiography. Beta-receptor blockers, ACE-inhibitors, Calcium channel inhibitors and other drugs were given at the discretion of the responsible physician.

Vector-ECG. Immediately after the start of treatment, monitoring with continuous vector-ECG was started and continued until the coronary angiography was done after 20–28 h. Vector-ECG was recorded by the 8 lead MIDA-system (Ortius). The recordings were stored on diskettes and evaluated by two external experts without any knowledge of patient's characteristics and randomization. A reduction of ST vector magnitude (STVM), >50% if STVM was >200 μV during the initial 120 min or a reduction of STVM >25% if STVM was 100–200 μV from the start, was regarded as indicator of early reperfusion (17). Ischemic episodes were defined as a reversible increase of STVM >50 μV from the patient's own baseline for >1 min (18).

Blood samples. Blood samples including myoglobin were obtained just prior the start of treatment and after 90 min. Myoglobin was analyzed by a radioimmunoassay (19). A relative increase of myoglobin T90-TO/TO >4 (20) or a slope of increase of myoglobin >150 $\mu\text{g/L/h}$ (21) were taken as signs of reperfusion.

Coronary angiography. Coronary angiography was performed 20–28 h after inclusion and 8–16 h after the last injection of the study drug. Five respectively three standardized projections of the left and right coronary arteries were used and recorded with 35 mm cinefilm. The evaluation was made retrospectively by consensus of two radiologists without knowledge of the randomized groups. The primary efficacy variable was TIMI grade in the infarct-related artery which was identified in relation to ECG-changes.

Safety. Major bleeding was defined as a decrease in the hemoglobin level of >20 g/L in connection with clinical

symptoms, need of transfusion of blood, muscle or joint bleeding, intracranial bleeding, interruption of treatment because of bleeding or death caused by bleeding. Minor bleeding was defined as a decrease in the hemoglobin level of >20 g/L without signs of bleeding or any bleeding that did not meet any of the criteria for major bleeding.

Clinical events and follow up. Recorded clinical events were death, myocardial reinfarction or revascularization. Myocardial infarction was defined according to WHO criteria. Revascularization, percutaneous coronary angioplasty (PTCA) or coronary artery bypass grafting (CABG) was only performed if there was spontaneous or exercise induced ischemia.

Each patient stayed in hospital during the acute phase. The study treatment was only given twice (until the coronary angiography). The patients had a final follow-up visit after 14–21 days.

Statistics. All randomized patients were included in the evaluation of safety and clinical events. The evaluation of the differences in the TIMI grade 3 flow could obviously only be analyzed in patients with coronary angiograms. Conventional chi-square tests were used to compare the treatment groups. In cases with less than five expected in any cells, Fischer test was used to evaluate significances. P values less than 0.05 in two tailed tests were considered to indicate significance.

RESULTS

One hundred one patients, 71 males and 30 females were included in the study. The median age was 67 years (37–78). There were some (nonsignificant) differences in the baseline characteristic between the dalteparin-treated (54) and the placebo-treated (47) groups in this small material (Table 1). Coronary angiography was performed in 93 of 101 patients and 56 patients had TIMI grade 3 flow, 16 grade 2 flow, 1 grade 1 flow and 20 grade 0 flow in the infarct-related artery after 20–28 h. Of the eight patients without coronary angiography, three died before the planned investigation (all 3 from the placebo group), and five had contraindications. Myoglobin levels were analyzed in 97 patients. Adequate vector-ECG recordings were obtained in 76 patients. In the other 25 patients, recordings were either inadequate (n = 5) or not performed for various reasons.

Dalteparin added to streptokinase and aspirin had no effect on the noninvasive indicators of early reperfusion, evaluated by the rise of myoglobin during 90 min or the regression of ST-elevation at vector-ECG during 120 min (Table 2).

Concerning the primary aim, the dalteparin group tended to have a higher rate of TIMI grade 3 flow in the infarct-related arteries at the time of coronary angiography (Table 3). Assuming that the three patients who died before the scheduled angiogram had TIMI grade 0–1 flow, there would be a significant (p = 0.045) difference between the

Table 1. Baseline Characteristics

	Placebo n = 47	Dalteparin n = 54
Patients Characteristics		
Male	77	65
Age (years)	64 (41–78)	68 (54–77)
Body weight (kg)	78 (55–130)	78 (51–104)
Risk Factors %		
Current smoker	30	35
Hypertension	36	18
Dyspnea	13	11
Diabetes mellitus	13	7
Previous myocardial infarction	11	17
Angina >1 month	23	22
Chest pain during the last 24 h	34	32
UAP <1 month	36	30
Medication At Entry %		
Aspirin	19	13
Betablockers	26	11
Digitalis	8	2
ACE-Inhibitors	14	2
Diuretics	19	15
Calcium Antagonists	19	13
Nitrates	11	9
Medication at Follow up %		
Aspirin	88	92
Lipid Lowerers	5	4
Betablockers	85	88
ACE-Inhibitors	24	40
Nitrates	17	12

groups. In patients with signs of early reperfusion based on myoglobin, there was a significantly higher rate of TIMI grade 3 flow after 20–28 h in the infarct-related arteries in the dalteparin group compared with the placebo group (Table 3). Also in patients with vector-ECG signs of early reperfusion, there tended to be a higher frequency of TIMI grade 3 flow in the infarct-related arteries in the dalteparin group but the difference was not significant (Table 3).

The rate of patients with postthrombotic ischemic episodes registered on vector-ECG the first 24 h after the thrombolytic treatment tended to be lower in the dalteparin group compared with the placebo group. Excluding the initial 6 h of unstable coronary blood flow early after thrombolysis, the rate of ischemic episodes was significantly lower in the dalteparin group and especially in patients with vector-ECG signs of early reperfusion (Table 4).

Clinical outcome and safety. There was no significant difference in clinical outcome between the two groups. There were no cerebral bleedings. Five of the six bleedings occurred in the dalteparin group and most of them were minor (hematoma related to the puncture sites in the femoral arteries). There were more reinfarctions in the dalteparin group and five of eight occurred between 24–72 h after termination of dalteparin. Regarding deaths and revascularization, there were no differences (Table 5).

Table 2. Noninvasive Signs of Reperfusion

	Placebo	Dalteparin	n	p
Myoglobin, relative increase*	18/45 (40%)	16/52 (31%)	97	0.34
Myoglobin, slope increase†	26/45 (58%)	30/52 (58%)	97	0.99
Vector-ECG‡	26/33 (79%)	30/43 (70%)	76	0.38

*T90-T0/T0 > 4 (20); †>150 ug/L/h (21); ‡A reduction of STVM, >50 %/120 min or >25%/120 min if STVM was >200 uV or >100 uV (17)

DISCUSSION

This is the first study that evaluates the influence of lmw-heparin in addition to streptokinase and aspirin on early reperfusion and patency in acute myocardial infarction with ST-elevation. Two previous dose-finding studies with 20 and 76 patients, respectively, have indicated that dalteparin at present dosages in combination with streptokinase might be safe (only minor bleedings and no cerebral bleedings) (15,22). In another study it was shown that lmw-heparin given to patients with acute myocardial infarction starting at day 5 and continuing for 3 weeks after streptokinase and intravenous standard heparin reduced cardiac events and also seemed to be safe (16). The golden standard to show patency is still coronary angiography. However, indications of early reperfusion can be obtained by vector-ECG or continuous 12-lead ECG (17,23). Another alternative in monitoring frequent blood samples demonstrates a rapid increase in levels of biochemical markers (20,21).

In this pilot of trial patients with acute myocardial infarction treated with streptokinase and aspirin, there was a tendency of a higher rate of TIMI grade 3 flow in the infarct-related artery after 24 h in the dalteparin group. However, in the post-hoc analysis of subgroups of patients with noninvasive signs of early reperfusion, the improvement of TIMI grade 3 flow at 24 h was statistically significant which might indicate that dalteparin maintains patency in the thrombolized artery. Furthermore, the indication of improvement in coronary blood flow was supported by less postthrombolytic ischemic episodes in the dalteparin group.

Choice of thrombolytic agent. The benefit with thrombolytic treatment is obvious in patients with ST-elevations

or LBBB and onset of symptoms within the last 12 hours. The choice of fibrinolytic regimen seems to be less important for the overall probability of stroke-free survival, as the fibrin specific regimens that provide more rapid reperfusion raises the risk of cerebral hemorrhage (24). Thus, the GUSTO-I trial provided evidence that early and complete thrombolysis is closely associated with better clinical outcome and that there was a 14% relative 30-day survival benefit of t-PA compared with streptokinase (4). However, in the two previous large scale trials, Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI-2) and International Study of Infarct Survival (ISIS-3), there were no significant differences between streptokinase and t-PA in hospital or 35-days mortality (25,26). As the clinical difference in efficacy between the different thrombolytic regimes might be considered marginal in many patients, streptokinase is still widely used because of the lower cost. If early reperfusion and patency of streptokinase could be improved by the combination with adjuvant antithrombotic agents, e.g., lmw-heparin, this might be an attractive alternative routine treatment as adjuvant to thrombolysis.

Heparin as adjuvant to thrombolysis. The need for heparin as an adjuvant to thrombolytic treatment is not well documented. In the short-term perspective, heparin seems to reduce reocclusion rate of opened infarct-related arteries (10,27) and especially in combination with t-PA as shown in Global Utilization of Streptokinase and t-PA for Occluded Arteries (GUSTO-I) (4). However, the long-term effects of heparin, intravenous or subcutaneous, in addition to streptokinase and aspirin are not clear. Available evidence from clinical trials does not necessitate the routine addition of heparin to aspirin and streptokinase in acute myocardial

Table 3. TIMI Grade 3 Flow in Infarct-Related Arteries in All Patients and in Subgroups With Noninvasive Signs of Reperfusion Treated with Placebo versus Dalteparin

TIMI Grade 3 Flow 20-28 h After Start of Thrombolysis				
	Placebo	Dalteparin	n	p
All patients with angiography	22/43 (51%)	34/50 (68%)	93	0.10
Noninvasive signs of early reperfusion:				
Myoglobin, relative increase*	9/18 (50%)	11/13 (85%)	31	0.066
Myoglobin, slope increase†	12/26 (46%)	20/27 (74%)	53	0.038
Vector-ECG‡	12/23 (52%)	22/30 (73%)	53	0.11

*T90-T0/T0 >4 (20); †>150 ug/L/h (21); ‡A reduction of STVM, >50%/120 min or >25%/120 min if STVM was >200 uV or >100 uV (17)

Table 4. Postthrombolytic Ischemic STVM Episodes 0-24 Hours and 6-24 Hours in All Patients and in Subgroups with Noninvasive Signs of Reperfusion

	Placebo	Dalteparin	n	p
0-24 hours				
All, patients with VCG	13/32 (41%)	11/43 (26%)	n = 75	0.17
Reperfusion signs with Myo*	5/13 (38%)	2/12 (17%)	n = 25	0.38
Reperfusion signs with Myo†	7/18 (39%)	7/24 (29%)	n = 42	0.51
Reperfusion signs with VCG‡	11/24 (46%)	7/29 (24%)	n = 53	0.10
6-24 hours				
All, patients with VCG	12/32 (38%)	7/43 (16%)	n = 75	0.037
Reperfusion signs with Myo*	5/13 (38%)	1/12 (8%)	n = 25	0.16
Reperfusion signs with Myo†	7/18 (39%)	5/24 (21%)	n = 42	0.20
Reperfusion signs with VCG‡	10/24 (42%)	3/29 (10%)	n = 53	0.01

Myo = myoglobin; VCG = vector-ECG; *T90-T0/T0 > 4 (20); †>150 ug/L/h (21); ‡A reduction of STVM, >50%/120 min or >25%/120 min if STVM was >200 uV or >100 uV (17)

infarction (24-26,28). The short-term effect that is seen during heparin infusion tends to disappear early after discontinuation because of an increased rate of recurrent unstable angina, myocardial infarction and urgent interventions. This reactivation phenomenon has been described early after discontinuation of intravenous heparin, both in unstable angina (29-31) and after thrombolysis (14). Therefore, there is no routine using heparin in addition to streptokinase and aspirin in many countries in northern Europe which also are in accordance with recent American treatment guidelines (32).

Hirudin and hirulog are other alternative treatments as an adjuvant to thrombolysis to improve patency in the infarct-related artery and clinical outcome in patients with acute myocardial infarction. The first trials with hirudin and hirulog showed promising results (33-36). Also, the TIMI 9B and GUSTO IIB trials showed an early reduction of reinfarctions although this difference was decreased by time and the bleeding rate was elevated in comparison to heparin (37,38).

Lmw-heparin. Compared to standard heparin, lmw-heparin has several advantages, i.e., a longer half-life, a greater and more predictable bioavailability and no need for

laboratory monitoring. Today there is no doubt that lmw-heparin is an effective alternative to heparin as prophylactic of deep vein thrombosis when administered by the subcutaneous route (39). Dalteparin had also reduced the rate of left ventricle thrombosis in post myocardial infarction patients (40). In the placebo controlled Fragmin during Instability in Coronary Artery Disease (FRISC) study, dalteparin twice daily in addition to aspirin reduced the risk of death and myocardial infarction by more than 50% compared with aspirin alone during the first five days. However, early after reduction of the dalteparin dose there were signs of reactivation (30). In later studies subcutaneous lmw-heparin has been shown to be at least as effective as intravenously standard heparin in the acute phase of unstable coronary disease (41,42).

Lmw-heparin as adjuvant to thrombolysis. Lmw-heparin might be a convenient alternative to heparin as an adjuvant to thrombolysis. The effect of lmw-heparin after thrombolysis has so far only been investigated in one published study. In that trial streptokinase and five days of heparin was given followed by three weeks of lmw-heparin treatment which reduced the rate of reinfarction and angina (16). In a recent dose finding study, it was shown that dalteparin in increasing dosages up to 100 IU/kg subcutaneously twice daily together with streptokinase gave a rapid rise and dose-dependent activity of antifactor Xa (15).

In the present study dalteparin was only given twice before the coronary angiography was performed. During the dalteparin treatment there were several signs of improvement in coronary blood flow. However, during follow-up there were eight and two reinfarctions in the dalteparin and placebo groups, respectively. In five of the eight patients in the dalteparin group, the reinfarction occurred between 24-72 h after termination of dalteparin suggesting a reactivation of the thrombotic process. There were no differences in the rate of intervention or death between the two groups. The treatment was well tolerated and the only side effect was somewhat more puncture-related bleedings in the dalteparin group.

Table 5. Clinical Events Until Follow Up Day 21

	Placebo (n = 47)	Dalteparin (n = 54)
Bleeding Total	1	5
Major	0	2
Minor	1	3
Death	6	4
Reinfarction	2	8
Revascularization	12	10
PTCA	8	8
CABG	4	2
Total cardiac events	20	22
Number of patients with cardiac events	18	15

Noninvasive indicators of early reperfusion. In previous studies the rate of TIMI grade 3 flow after 90 min and 24 h was reported to be about 30% and 50%, respectively, in patients treated with streptokinase, including those with spontaneous reperfusion (3,43). This corresponds fairly well with the 60% TIMI grade 3 flow in the infarct-related artery after 24 h in the total group of 93 that underwent angiography in the present study. The noninvasive sign of reperfusion using the relative increase of myoglobin (20) suggested 35% rate of early reperfusion compared to the slope increase of myoglobin (21) which indicated a higher and maybe a more realistic rate of early reperfusion (58%), at 90 min. Vector-ECG indicated an optimistic rate of early reperfusion of 74% after 120 min. Unfortunately no early coronary angiograms at 90 min were performed, which make the noninvasive results difficult to validate. Although the noninvasive indicators of reperfusion are uncertain, there were no indications of any effects of the lmw-heparin treatment on early reperfusion. This might be related to the use of only subcutaneous injections, since a therapeutic level of antifactor-Xa activity is not reached until around 1-2 h after the first dose of lmw-heparin (15). In order to explore possible early benefits of lmw-heparin, an intravenous bolus dose will be needed.

Limitations. In the present study, lmw-heparin/placebo treatment was only given twice until the coronary angiography was done after 20-28 h. It might have been preferable to maintain the treatment for a longer time to stabilize the lesion and the coagulation system in order to avoid the risk of reactivation. The evaluation of early reperfusion after 90 min would have been more reliable if an early angiography was performed, especially as the noninvasive markers of reperfusion gave variable results. The fact that the lmw-heparin group had a lower rate of drug treatment, known hypertension and diabetes at inclusion, indicating a less severe disease and that there was a higher frequency of smokers might have influenced the results although the differences in baseline characteristics between the two groups were not significant. The very small sample size implies that this pilot trial should be interpreted cautiously as the confidence intervals regarding all analyses are wide.

Future and implications. Lmw-heparin might be an attractive, safe, convenient and potent adjuvant treatment to thrombolysis and aspirin in patients with acute myocardial infarction. The additive effect of lmw-heparin might contribute to a higher rate of opened infarct-related arteries, avoid reocclusion episodes and improve maintenance of coronary blood flow. In future studies prolonged treatment with the lmw-heparin treatment should be investigated if late reocclusions and reactivation might be prevented. Furthermore it would probably be advantageous to start with an intravenous bolus injection to investigate whether lmw-heparin also might improve early reperfusion. Further larger studies are needed to evaluate the efficacy of lmw-heparin as an adjuvant treatment to thrombolysis and aspirin.

Acknowledgments

We want to acknowledge the enthusiastic and great work done by the research nurses and especially Anita Ahlfelt, Gerd Källström, Eva Phil and Gerd Åhlsjö.

Reprint requests and correspondence: Dr. Gunnar Frostfeldt, Department of Cardiology, University Hospital, S-751 85 Uppsala, Sweden. E-mail: Gunnar.Frostfeldt@medicin.uu.se.

REFERENCES

1. The GUSTO Angiographic Investigators. The effects of tissue plasminogen activator, streptokinase, or both on coronary-artery patency, ventricular function, and survival after acute myocardial infarction. *N Engl J Med* 1993;329:1615-22.
2. Fibrinolytic Therapy Trialists' (FTT) Collaborative Group. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomised trials of more than 1000 patients. *Lancet* 1994;343:311-22.
3. Barbagelata NA, Granger CB, Oqueli E, et al. TIMI grade 3 flow and reocclusion after intravenous thrombolytic therapy: a pooled analysis. *Am Heart J* 1997;133:273-82.
4. Simes RJ, Topol EJ, Holmes DR Jr, et al. Link between the angiographic substudy and mortality outcomes in a large randomized trial of myocardial reperfusion. Importance of early and complete infarct artery reperfusion. GUSTO-I Investigators. *Circulation* 1995;91:1923-8.
5. Karagounis L, Sorensen SG, Menlove RL, Moreno F, Anderson JL. Does thrombolysis in myocardial infarction (TIMI) perfusion grade 2 represent a mostly patent artery or a mostly occluded artery? Enzymatic and electrocardiographic evidence from the TEAM-2 study. Second Multicenter Thrombolysis Trial of Eminase in Acute Myocardial Infarction. *J Am Coll Cardiol* 1992;19:1-10.
6. Anderson JL, Karagounis LA, Becker LC, et al. TIMI perfusion grade 3 but not grade 2 results in improved outcome after thrombolysis for myocardial infarction. Ventriculographic, enzymatic, and electrocardiographic evidence from the TEAM-3 Study. *Circulation* 1993;87:1829-39.
7. Stadium ML. Angiographic monitoring of reperfusion therapy for acute myocardial infarction. TIMI grade 3 perfusion is the goal [editorial]. *Circulation* 1993;87:2055-7.
8. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. *Lancet* 1988;2:349-60.
9. Roux S, Christeller S, Ludin E. Effects of aspirin on coronary reocclusion and recurrent ischemia after thrombolysis: a meta-analysis. *J Am Coll Cardiol* 1992;19:671-7.
10. Bleich SD, Nichols TC, Schumacher RR, et al. Effect of heparin on coronary arterial patency after thrombolysis with tissue plasminogen activator in acute myocardial infarction. *Am J Cardiol* 1990;66:1412-7.
11. Mahaffey KW, Granger CB, Collins R, et al. Overview of randomized trials of intravenous heparin in patients with acute myocardial infarction treated with thrombolytic therapy. *Am J Cardiol* 1996;77:551-6.
12. Williams MJ, Morison IM, Parker JH, Stewart RA. Progression of the culprit lesion in unstable coronary artery disease with warfarin and aspirin versus aspirin alone: preliminary study. *J Am Coll Cardiol* 1997;30:364-9.
13. O'Connor CM, Meese R, Carney R, et al. A randomized trial of intravenous heparin in conjunction with anistreplase (anisoylated

- plasminogen streptokinase activator complex) in acute myocardial infarction: the Duke University Clinical Cardiology Study (DUCCS) 1. *J Am Coll Cardiol* 1994;23:11-8.
14. Granger CB, Hirsch J, Califf RM, et al. Activated partial thromboplastin time and outcome after thrombolytic therapy for acute myocardial infarction: results from the GUSTO-I trial. *Circulation* 1996;93:870-8.
15. Strandberg LE, Kahan T, Lundin P, et al. Anticoagulant effects of low-molecular-weight heparin following thrombolytic therapy in acute myocardial infarction: a dose-finding study. *Haemostasis* 1996;26:247-57.
16. Glick A, Kornowski R, Michowich Y, et al. Reduction of reinfarction and angina with use of low-molecular-weight heparin therapy after streptokinase (and heparin) in acute myocardial infarction. *Am J Cardiol* 1996;77:1145-8.
17. Dellborg M, Topol EJ, Swedberg K. Dynamic QRS complex and ST segment vectorcardiographic monitoring can identify vessel patency in patients with acute myocardial infarction treated with reperfusion therapy. *Am Heart J* 1991;122:943-8.
18. Dellborg M, Gustafsson G, Riha M, Swedberg K. Dynamic changes of the QRS complex in unstable angina pectoris. *Int J Cardiol* 1992;36:151-62.
19. Roxin LE, Venge P, Wide L. A fast and sensitive radioimmunoassay of human myoglobin for use in the early diagnosis of heart infarction. *Clin Chim Acta* 1980;107:129-34.
20. Laperche T, Steg PG, Dehoux M, et al. A study of biochemical markers of reperfusion early after thrombolysis for acute myocardial infarction. The PERM Study Group. Prospective Evaluation of Reperfusion Markers. *Circulation* 1995;92:2079-86.
21. Zabel M, Hohnloser SH, Koster W, et al. Analysis of creatine kinase, CK-MB, myoglobin, and troponin T time-activity curves for early assessment of coronary artery reperfusion after intravenous thrombolysis. *Circulation* 1993;87:1542-50.
22. Nesvold A, Kontny F, Abildgaard U, Dale J. Safety of high doses of low molecular weight heparin (Fragmin) in acute myocardial infarction. A dose-finding study. *Thromb Res* 1991;64:579-87.
23. Krucoff MW, Croll MA, Pope JE, et al. Continuous 12-lead ST-segment recovery analysis in the TAMI 7 study. Performance of a noninvasive method for real-time detection of failed myocardial reperfusion. *Circulation* 1993;88:437-46.
24. Collins R, Peto R, Baigent C, Sleight P. Aspirin, heparin, and fibrinolytic therapy in suspected acute myocardial infarction. *N Engl J Med* 1997;336:847-60.
25. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico. GISSI-2: a factorial randomised trial of alteplase versus streptokinase and heparin versus no heparin among 12,490 patients with acute myocardial infarction. *Lancet* 1990;336:65-71.
26. ISIS-3 (Third International Study of Infarct Survival) Collaborative Group. ISIS-3: a randomised comparison of streptokinase vs. tissue plasminogen activator vs. anistreplase and of aspirin plus heparin vs. aspirin alone among 41,299 cases of suspected acute myocardial infarction. *Lancet* 1992;339:753-70.
27. de Bono DP, Simoons ML, Tijssen J, et al. Effect of early intravenous heparin on coronary patency, infarct size, and bleeding complications after alteplase thrombolysis: results of a randomised double blind European Cooperative Study Group trial. *Br Heart J* 1992;67:122-8.
28. Collins R, MacMahon S, Flather M, et al. Clinical effects of anticoagulant therapy in suspected acute myocardial infarction: systematic overview of randomised trials. *BMJ* 1996;313:652-9.
29. Theroux P, Waters D, Lam J, et al. Reactivation of unstable angina after the discontinuation of heparin [see comments]. *N Engl J Med* 1992;327:141-5.
30. FRISC study group. Low-molecular-weight heparin during instability in coronary artery disease. Fragmin during Instability in Coronary Artery Disease. *Lancet* 1996;347(9001):561-8.
31. Granger CB, Miller JM, Bovill EG, et al. Rebound increase in thrombin generation and activity after cessation of intravenous heparin in patients with acute coronary syndromes. *Circulation* 1995;91:1929-35.
32. ACC/AHA Guidelines for the Management of Patients With Acute Myocardial Infarction. *J Am Coll Cardiol* 1996;28:1328-1428.
33. Cannon CP, McCabe CH, Henry TD, et al. A pilot trial of recombinant desulfatohirudin compared with heparin in conjunction with tissue-type plasminogen activator and aspirin for acute myocardial infarction: results of the Thrombolysis in Myocardial Infarction (TIMI) 5 trial. *J Am Coll Cardiol* 1994;23:993-1003.
34. Lee LV. Initial experience with hirudin and streptokinase in acute myocardial infarction: results of the Thrombolysis in Myocardial Infarction (TIMI) 6 trial. *Am J Cardiol* 1995;75(1):7-13.
35. Theroux P, Perez-Villa F, Waters D, Lesperance J, Shabani F, Bonan R. Randomized double-blind comparison of two doses of Hirulog with heparin as adjunctive therapy to streptokinase to promote early patency of the infarct-related artery in acute myocardial infarction. *Circulation* 1995;91(8):2132-9.
36. White HD, Aylward PE, Frey MJ, et al. Randomized, double-blind comparison of hirulog versus heparin in patients receiving streptokinase and aspirin for acute myocardial infarction (HERO). Hirulog Early Reperfusion/Occlusion (HERO) Trial Investigators. *Circulation* 1997;96:2155-61.
37. Antman EM. Hirudin in acute myocardial infarction. Thrombolysis and Thrombin Inhibition in Myocardial Infarction (TIMI) 9B trial [see comments]. *Circulation* 1996;94:911-21.
38. GUSTO IIb investigators. A comparison of recombinant hirudin with heparin for the treatment of acute coronary syndromes. The Global Use of Strategies to Open Occluded Coronary Arteries. *N Engl J Med* 1996;335:775-82.
39. Barrowcliffe TW. Low molecular weight heparin(s). *Br J Haematol* 1995;90:1-7.
40. Kontny F, Dale J, Abildgaard U, Pedersen TR. Randomized trial of low molecular weight heparin (dalteparin) in prevention of left ventricular thrombus formation and arterial embolism after acute anterior myocardial infarction: the Fragmin in Acute Myocardial Infarction (FRAMI) Study. *J Am Coll Cardiol* 1997;30:962-9.
41. Cohen M, Demers C, Gurfinkel EP, et al. A comparison of low-molecular-weight heparin with unfractionated heparin for unstable coronary artery disease. Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events Study Group. *N Engl J Med* 1997;337:447-52.
42. Klein W, Buchwald A, Hillis SE, et al. Comparison of low-molecular-weight heparin with unfractionated heparin acutely and with placebo for 6 weeks in the management of unstable coronary artery disease. Fragmin in unstable coronary artery disease study (FRIC). *Circulation* 1997;96:61-8.
43. Chesebro JH, Knatterud G, Roberts R, et al. Thrombolysis in Myocardial Infarction (TIMI) Trial, Phase I: a comparison between intravenous tissue plasminogen activator and intravenous streptokinase. Clinical findings through hospital discharge. *Circulation* 1987;76:142-54.